UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/825,713	04/04/2001	Matthew During	DUR01-NP001	3131

21125 7590 12/04/2003

NUTTER MCCLENNEN & FISH LLP
WORLD TRADE CENTER WEST
155 SEAPORT BOULEVARD
BOSTON, MA 02210-2604

EXAMINER	
GUZO, DAVID	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 12/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/825,713	DURING ET AL.	
	Examiner	Art Unit	
	David Guzo	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,8,10-13,16 and 20-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 8, 10-13, 16, 20-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☒ Interview Summary (PTO-413) Paper No(s). *1*.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Detailed Action

The requirement for a supplemental Declaration is withdrawn in view of the application data sheet filed 9/5/03.

The 35 USC 102(b) rejection over Eglitis et al. is withdrawn in view of applicants' amendments to the claims.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 8, 10-13, 16, 20-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As a preliminary matter, it is noted that the scope of enablement rejection previously made against claims 1-4, 8-13, 16 and 17 in the previous Office Action is withdrawn. The previous indication that the claims were enabled for a method of treating rats or mice comprising administering a therapeutically effective amount of mammalian stem cells capable of differentiating into neuronal cells to said rats or mice was in error because the instant specification does not provide a practical use for

treating rats or mice for diseases of the nervous system. The specification clearly indicates that artificially created rat or mouse models of neurological diseases or trauma are used as experimental systems to study neurological diseases or trauma in humans or to test potential treatments of said diseases or trauma in humans. The only contemplated use for the claimed invention is for treatment of disorders or diseases of, or trauma to, the nervous systems of mammals. However, the grounds of rejection (*Wands* factor analysis), as it applies to methods of treating humans, is reapplied in the context of an enablement rejection against all claims. Also, an additional analysis of the *Wands* factors in light of the new rejection is presented below.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is required is not based upon a single factor, but rather is a conclusion reaches by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and include the following: 1) Unpredictability of the art. The art in the area of use of mammalian stem cells of myeloid origin (i.e. hematopoietic stem cells) to treat diseases of, or trauma to, the nervous system is highly unpredictable. Applicants' invention appears to be based upon preliminary observations that, in mice and humans, introduced adult bone marrow stem cells are apparently capable of crossing the blood-brain barrier and differentiating into neurons (See Mezey et al. Science, 2000, Vol. 290, pp. 1779-1782 and Mezey et

al. PNAS, 2003, Vol. 100, No. 3, pp. 1364-1369). However, these preliminary observations do not involve therapy for any nervous system disorder or trauma in humans or other mammals but instead represent only very preliminary basic scientific studies that confirm the concept that introduced adult bone marrow stem cells can differentiate into neurons in mice and humans. Indeed, in the Mezey et al. article presenting human data, said data was derived from examination of postmortem brain samples of female patients (suffering from a variety of **non-neurological diseases**) who had received bone marrow transplants from male donors. The human data show that a very small number of stem cells appear to be able to migrate into the brain and nervous system (a maximum of 7 new neurons derived from the introduced stem cells per 10,000 neurons examined) and differentiate into neurons. Mezey et al. noted that the factors which govern how many stem cells can cross the blood brain barrier and differentiate into neurons are not known and the factors which govern where in the nervous system the stem cells migrate are not known. Mezey et al. also notes that much additional research remains to be conducted before bone marrow derived stem cells could be used to treat neurological diseases in humans.

Additionally, with regard to the unpredictability of the art, it is noted that the claims encompass treatments of neurological diseases such as Alzheimer's disease, multiple sclerosis, etc. wherein it is unclear how the introduction of adult hematopoietic stem cells can result in effective treatment.

2) State of the art. The use of adult hematopoietic stem cells to treat diseases of, or trauma to, the nervous system is nil.

3) Number of working examples. Applicants present no working examples of the claimed invention involving treatment of naturally occurring disorders or diseases of the nervous system. It is noted that applicants present some data involving treatment of induced neurological damage in rat or mouse models of Parkinson's disease wherein adult stem cells are introduced into the nervous system and wherein said stem cells differentiate into neurons and appear to alleviate some symptoms of the induced disease condition. However, the relevance of this data to the treatment of naturally occurring neurological diseases (i.e. Parkinson's disease) in humans or other mammals is unclear (See "Amount of guidance provided by applicants" section below).

4) Amount of guidance provided by applicants. As noted above, applicants provide data concerning treatment of induced neurological damage in Parkinsonian rats. However, the relevance of this data to treatment of naturally occurring disease conditions (Parkinson's disease) in humans or other mammals is unclear. The problems with using data obtained in rat models of Parkinson's disease are exemplified by Kim et al. (Nature, 2002, Vol. 418, pp. 50-56). Kim et al. obtained some beneficial responses in treating Parkinsonian rats by administration of embryonic stem cells which differentiate into dopamine neurons. However, Kim et al. noted that further studies were needed both in rodent and primate systems to address the long-term safety and efficacy of these cells and that therapeutic benefits that can be derived from use of ES cells are not current but are an ultimate goal of the research. Additionally, Dr. McKay, a co-author of the Kim et al. paper, noted that results which suggest that ES cells can be used to treat Parkinson's disease are preliminary and that researchers "...need much more

information about how the cells interact with the host brain and about their safety before similar strategies can be tested in humans." Clearly, researchers in the field make no claims that stem cells (either adult hematopoietic or embryonic) can currently be used to treat any neurological disease. Finally, it is noted that applicants present no data or guidance on how the instantly recited stem cells can be used to treat neurological diseases such as Alzheimer's disease, multiple sclerosis, ALS, etc.

5) Scope of the invention. The scope of the invention is broad and reads on treatment of any neurological disease or disorder or trauma in any mammal.

6) Nature of the invention. The invention involves a complex, poorly understood area of medicine, molecular biology; the use of stem cells to generate neurons in vivo so as to treat neurological diseases or trauma.

7) Level of skill in the art. The credentials of those of skill in the art is high (i.e. Ph.D.s and/or M.D.s); however, the level of skill in the art must be considered to be low because those of skill in the art have been unable to reduce to practice the treatment of any neurological disease using stem cells.

Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be considered that the skilled artisan would have had to have conducted undue and excessive experimentation in order to practice the claimed invention.

Given the new grounds of rejection, applicants arguments directed to the now withdrawn scope of enablement rejection are moot. However, applicants' points of argument, as they pertain to the instant enablement rejection, will be addressed.

First, applicants argue (in response to the previous examiner's indication that reliance upon the teachings of the article by Mezey et al. (2003) to establish the state of the art at the time of applicants invention was inappropriate) that the human results presented in the Mezey et al. (PNAS, 2003) paper followed directly from the first Mezey et al. (Science, 2000) paper, thus showing that a lab using methods similar to those used by applicants could go from mice to humans in two years. Applicants thus conclude that using the claimed methods in humans is a straightforward application of the instant disclosure and that the human data was obtained without undue experimentation.

In response, the examiner notes that to the extent that the Mezey et al. article shows that hematopoietic stem cells can give rise to neurons in humans, the Mezey et al. reference can be used to support applicants' arguments as to the validity of the underlying concept of applicants invention. However, it is noted that applicants invention involves the administering of a therapeutically effective amount of stem cells of myeloid origin in order to treat a neurological disease, disorder or trauma. The Mezey et al. (PNAS, 2003) article does not teach any therapeutic method for treating any neurological disease. Indeed, the Mezey et al. reference involves postmortem observations that bone marrow stem cells administered to patients suffering from various non-neurological diseases can apparently enter the nervous system and a small

number (maximum of 7 stem cells per 10,000 neurons) can differentiate into neurons. Mezey et al. did not indicate that the neurons derived from stem cells could treat any neurological disease. Mezey et al. only postulate that after extensive further experimentation, future attempts may be made to try to treat neurological diseases in patients. Therefore, any arguments that Mezey et al. (2003) provides enablement for the therapeutic use of bone marrow stem cells to treat any or all neurological diseases are inconsistent with the teachings of the reference.

Second, applicants indicate that the Mezey et al. experiments demonstrate that well characterized animal models can be used to successfully predict human results without undue experimentation.

In response, the examiner notes that the Mezey et al. experiments do not teach a method of treating any neurological disease in humans or mammals. Mezey et al. (2000 and 2003) only recite the possibility of using adult stem cells at some point in the future after further extensive experimentation. This hardly represents an enabling disclosure. The problems associated with use of the current animal models of human neurological diseases, such as Parkinson's disease, to predict results which the skilled artisan would expect to see in humans are noted above.

Finally, applicants indicate that the instant specification teaches how to isolate progenitor and stem cells using markers which are found on human lineage committed progenitor cells as well as methods of culturing said cells and methods of transplanting the cultured stem cells into subjects.

In response, the examiner agrees with applicants' statements. However, the issue in the present case involves how the skilled artisan would use said cells to treat neurological diseases or trauma in mammals.

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Guzo, Ph.D., whose telephone number is (703) 308-1906. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 5:30 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, Ph.D., can be reached on (703) 305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

DAVID GUZO
PRIMARY EXAMINER

David Guzo
November 29, 2003